1083-138 Additive Effects of Statin Combined With Angiotensin Converting Enzyme Inhibitor on Vasomotion in Hypercholesterolemic Patients

Kwang K. Koh, Ji W. Son, Jeong Y. Ahn, Seung H. Han, Eak K. Shin, Gachon Medical School, Incheon, South Korea

Background: HMG-CoA reductase inhibitor, statins and ramipril prevented or retarded the progression of coronary heart disease in large-scaled, clinical studies. Endothelial function plays an important role in the pathogenesis of atherosclerosis. Because the mechanisms of the biological effects of statins and antiotensin converting enzyme inhibitor therapies differ, we studied the vascular responses to these therapies in hypercholesterolemic patients.
Methods: We administered simvastatin 20 mg and placebo or ramipril 10 mg daily during 2 months with washout 2 months to 32 hypercholesterolemic patients. This study was randomized, double-blind, placebo-controlled, crossover in design. *=P<0.05;**=P<0.01;***=P<0.001 vs. Baseline. Data= mean+SD. **Results**: Simvastatin alone or combined with ramipril significantly changed lipoproteins, and improved the percent flow-mediated dilator response (FMD) to hyperemia from 4.93±1.96 to 6.58±1.94 by 46±48% and from 4.66±1.66 to 6.78±1.95 by 59±66%, respectively (both P<0.001) and reduced plasma levels of nitrate from 88±44 to 75±32 uM by 0±52% and from 83±39 to 65±29 uM by 13±30%, respectively (P=0.183 and P=0.012, respectively), and plasma levels of malondialdehyde (MDA), a marker of free radical from 1.33±0.52 to 1.10±0.53 uM by 6±57% and from 1.34±0.60 to 1.01±0.41 uM by 13±47%, respectively (P=0.045 and P<0.001, respectively), compared with baseline measurements. However, simvastatin combined with ramipril changed to greater extent FMD and plasma levels of nitrate and MDA than simvastatin alone. **Conclusions:** Compared with simvastatin alone, added ramipril to simvastatin showed additive effects on flow-mediated dilation and the plasma levels of nitrate and MDA in hypercholesterolemic patients.

1083-139 Atorvastatin Suppresses the Expression of CD40 Ligand and P-Selectin on Platelets in Patients With Hypercholesterolemia

Yeo-Shin Hwang, Wen-Chan Tsai, Ching-Cheng Lin, Ye-Hsu Lu, Ying-Fu Chen, Chi-Kong Ho, Kaohsiung Medical College, Kaohsiung, Taiwan,ROC

Background: Hypercholesterolemia (HC), a risk factor for cardiovascular disease, is associated with inflammation and the prothrombotic state. Recently a CD40-CD40 ligand (CD40L) interaction and the activation of platelet was claimed to play a major role in the patheogenesis in atherosclerosis. The aim of the study was to characterize the in vitro expression of CD40L and p-selectin in patients with HC and to investigate whether atorvastatin (ATOR), a potent lipid-lowering agent, can influence the levels of these molecules and TNF-α.
Methods: Twelve patients with polygemic HC (total cholesterol > 220 mg/dl, or LDL > 130 mg/dl) without other associated inflammatory disease and 14 normal controls were enrolled in this study. Blood samples were obtained before and after 8 weeks of ATOR (10 mg/day) therapy in patient group. After isolation, half of the platelets were stimulated by the addition of ADP (5 μmol/L). Flow cytometry was used to analyze the expression of CD40L and p-selectin. TNF-α was measured by ELISA.
Results: The production of TNF-α is correlated with with VLDL (p= 0.002, R^2 = 0.50) and LDL/HDL ratio (p= 0.020, R^2 = 0.39). In normal controls, the expression of CD40L and p-selectin increased significantly after the stimulation of ADP. In patients, the expression of CD40L show no difference between with or without ADP stimulation before treatment (CD40L: 0.57 ± 0.55 vs 0.51 ± 0.19 mean fluorescence intensity [MFI] p= NS), but after 8 weeks of ATOR therapy, the addition of ADP can significantly increase the expression of CD40L (0.25 ± 0.17 vs 0.59 ± 0.45 MFI, p= 0.026). In the same time, after 8 weeks of ATOR therapy, the expression of CD40L and p-selectin decreased significantly (CD40L: 0.57 ± 0.55 vs 0.25 ± 0.17, p = 0.034; p-selectin: 2.3 ± 1.4 vs 1.06 ± 0.67, p= 0.006).
Conclusion: In this short term study, ATOR can down-regulate the expression of CD40L and p-selectin on platelets in patients with HC. We also found that the level of TNF-α was correlated with VLDL and LDL/HDL ratio. We supposed that in addition to its effect on decreasing the cholesterol level, ATOR can intervene the interaction of CD40-CD40L and the expression of p-selectin which may alleviate the prothrombotic potency of platelets in patients with HC.

1083-140 Ezetimibe Coadministered With Atorvastatin Compared to Atorvastatin Alone in the Attainment of Low-Density Lipoprotein Goals Among High-Risk Patients With Hypercholesterolemia

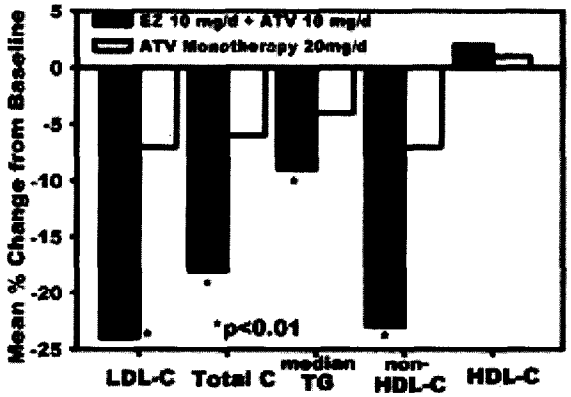
Evan A. Stein, Steen Stender, Pedro Mata, Damien Ponsonnet, Lorenzo Melani, Philip Sager, Leslie Lipka, Ramachandran Suresh, Enrico Veltri, Metabolic and Atherosclerosis Research Center, Cincinnati, OH, Schering-Plough Research Institute, Kenilworth, NJ

Background: This study evaluated ezetimibe (EZE) coadministered with atorvastatin (ATOR) in patients with heterozygous familial hypercholesterolemia, coronary heart disease, or multiple cardiovascular risk factors. **Methods:** After dietary stabilization, a 6- to 10-week washout, and ATOR run-in period (open-label ATOR 10 mg/day), 621 patients with baseline LDL-C ≥130 mg/dL and TG ≤350 mg/dL on ATOR 10 mg were randomized to two treatment arms; EZE 10 mg or additional double-blind ATOR (10 mg) administered daily for 4 weeks. The ATOR dose was doubled if LDL-C was >100 mg/dL after 4 and/or 9 weeks of treatment (maximum 80 mg/day with ATOR alone; 40 mg/day with coadministration). The primary endpoint was the proportion of patients achieving target LDL-C ≤100 mg/dL at week 14. **Results:** Addition of EZE to ATOR 10 mg/day followed by response-based titration of ATOR significantly increased the proportion of patients reaching target LDL-C to 22% (67/305) versus titration of ATOR alone of 7% (23/316; p<0.01). EZE+ATOR 10 mg significantly reduced LDL-C versus ATOR 20 mg at week 4 (22.8% versus 8.6%; p<0.01). In addition, despite only 60% of subjects in the EZE+ATOR group being on ATOR 40 mg (none on 80 mg) and 85% of ATOR group on 80 mg, the final (week 14) LDL-C reduction from randomization was 31.2% versus 18.9%, respectively. EZE+ATOR was well tolerated, with a safety profile similar to ATOR alone. **Conclusion:** Adding EZE to ongoing ATOR provides significantly greater LDL-C reduction than continued doubling of ATOR dose alone, and results in 3 times as many patients reaching target LDL-C. This offers a highly efficacious and well tolerated new treatment approach in hypercholesterolemia.

1083-141 Heterozygous Familial Hypercholesterolemia: Coadministration of Ezetimibe Plus Atorvastatin

William Vermaak, Xavier Pinto, Damien Ponsonnet, Philip Sager, Leslie Lipka, Ramachandran Suresh, Enrico Veltri, the Ezetimibe Study Group, University of Pretoria, Pretoria, South Africa, Schering-Plough Research Institute, Kenilworth, NJ

Background: Effective control of LDL-C in heterozygous familial hypercholesterolemia (HeFH) patients is difficult. This study evaluated the efficacy and safety of ezetimibe (EZE) coadministered with atorvastatin (ATV), in HeFH patients.
Methods: After dietary stabilization, a 6- to 10-week washout, and a ≥4-week ATV 10 mg/d run-in , 362 patients with LDL-C ≥130 mg/dL (mean LDL-C 197 mg/dL) and TG ≤350 mg/dL were randomized to EZE 10 mg/d or additional double-blind ATV 10 mg/d for 4 weeks. The ATV dose was doubled if LDL-C was >100 mg/dL after 4 and/or 9 weeks to a maximum of 80 mg/d with ATV alone and 40 mg/d with EZE + ATV. Endpoints were the proportion of patients achieving LDL-C ≤100 mg/dL at Week 14 and change in the lipid profile at 4 weeks.
Results: Coadministration of EZE with ATV 10 mg/d followed by response-based titration of ATV, significantly increased the proportion of patients reaching target LDL-C versus ATV monotherapy uptitration (17% vs 4%; p<0.01). EZE + ATV 10 mg significantly reduced LDL-C versus ATV 20 mg at Week 4 (23.6% versus 7.4%; p<0.01). Total-C, TG, and non-HDL-C were also significantly reduced (Figure). EZE + ATV was well tolerated, with a safety profile similar to ATV alone.
Conclusion: In HeFH patients, adding EZE to ATV provides significantly greater reduction in LDL-C and other lipid parameters than doubling the ATV dose alone, and results in four times as many patients achieving target LDL-C. EZE + ATV offers a highly efficacious and well tolerated therapeutic approach in HeFH.



1083-142 Ezetimibe Coadministered With Low Dose Statins in Primary Hypercholesterolemia: Lipid Profiles Comparable to High-Dose Statin Monotherapy

Philip Sager, Lorenzo Melani, Leslie Lipka, Alexandre Lebeaut, Ramachandran Suresh, Steven Sun, Enrico Veltri, the Ezetimibe Study Group, Schering-Plough Research Institute, Kenilworth, NJ

Background: Ezetimibe (EZE), a novel cholesterol absorption inhibitor, significantly lowers LDL-C and TG and raises HDL-C. The addition of EZE to low-dose statins may result in similar LDL-C reductions as achieved with high-dose statin monotherapy.
Methods: Data were analyzed from 4 Phase III, randomized, double-blind, Pbo-controlled studies in pts with primary hypercholesterolemia in which EZE 10mg + statin 10mg was compared with Pbo + higher doses of statin alone (simvastatin (S) 80mg, atorvastatin (A) 80mg, pravastatin (P) 40mg, or lovastatin (L) 40mg). After dietary stabilization (≥ NCEP Step I), a 2-12-wk screening/washout period and a 4-wk, Pbo lead-in period, pts with baseline LDL-C ≥145 to ≤250 mg/dl and TG ≤350 mg/dl were randomized to EZE + statin or Pbo + statin daily for 12 weeks.
Results: EZE + statin 10mg resulted in similar LDL-C reductions as those achieved with higher doses of statins alone (table) and comparable or greater effects on HDL-C and TG compared to statin monotherapy. The effects of EZE on LDL-C were independent of the statin tested. EZE had an excellent safety profile and was well tolerated.
Conclusion: The addition of EZE 10 mg to low doses of statins (10mg) provides similar effects on LDL-C, HDL-C, and TG, compared to high-dose statin monotherapy (S80mg, A80mg, P40mg, L40mg). The addition of EZE to statins provides an alternative to high-dose statins for therapy of hypercholesterolemia.
Percent Change from Drug Free Baseline to Endpoint